Estrogens, Aging, and Neurodegenerative Diseases

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Summary

Age is the greatest risk factor in Alzheimer's disease (AD) and Parkinson's disease (PD). Indications of a female bias in AD and of a male bias in PD have been often discussed but are not definitive. Moreover, evidence that estrogen replacement may be beneficial for AD and PD is also controversial. An unevaluated factor is how aging and cumulative estrogen exposure may modify brain responses to estradiol. Rodent models show that sustained exposure to estradiol can desensitize certain neuroendocrine responses.

Introduction

This review addresses the controversies in Alzheimer's disease (AD) and Parkinson's disease (PD) that concern sex differences and estrogen replacement therapy (ERT). In this essay, we prefer to use the term *sex differences* rather than *gender differences*: the latter, while deriving from effects of genes on sex chromosomes, is also strongly influenced by the individual's self-representation. First, we consider evidence on sex differences in AD and PD. Next, we briefly review the state of ERT in relation to AD and PD. Third, we consider how biological aging may be important in evaluating animal model studies of ERT, with recent examples as well as early work from our laboratory.

Age and sex in AD and PD

Age is the greatest risk factor in both AD and PD, this much is clear. Currently, the overall incidence and prevalence are better documented for AD than for PD. Both diseases are rare before the age of menopause.

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Dementia associated with AD is rare (<1%) before 60. Subsequently, the prevalence of dementia doubles about every five years and reaches the range of 5-50% by 85 years (Kawas and Katzman 1999; Kukull et al. 2002; Mayeux 2003; Suthers et al. 2003). This surprisingly wide range may be due to two major factors: heterogeneity within and between population (sociodemographic differences such as ethnicity, education, and income) and criteria for diagnosis. The dementia in AD can arise without stroke or cerebrovascular pathology (the "pure" cases). However, cerebrovascular-derived neuropathology (infarcts and lacunes) frequently co-exists with AD neuropathology in the same brains. For example, a large series with neuropathologically diagnosed AD had a 48% frequency of cerebrovascular pathology, versus 33% in non-AD brains (Jellinger and Mitter-Ferstl 2003). Hypertension is an important factor in stroke, varying widely between populations.

A general impression of female bias in dementia and AD is being challenged by better data on incidence and prevalence. Incidence refers to the frequency of new cases, whereas prevalence refers to the total number alive. Recent studies do not support early indications that women are at higher risk for dementia and AD than men (e.g., Kukull et al. 2002). Moreover, in Down' syndrome, males have a three-fold higher risk of dementia than females (Schupf et al. 1998), as discussed below. According to some studies, the greater prevalence of dementia in the general population of older women is mainly attributable to women's greater life expectancy, which at age 70 is about three years longer than for men in the industrial countries (Suthers et al. 2003). For example, at age 70, US women averaged 1.7 years with cognitive impairment, about 50% longer than the 1.1 years for men. This differential is compounded by the greater life expectancy of women at this age.

PD is about 90% less prevalent than dementia, but difficulties in diagnosis are well recognized (Tanner et al. 1997). Before 60 years of age, the prevalence of PD is <0.1%. Rapid increases after age 60 reach a prevalence of 1-3% by 85 years of age (de Rijk et al. 2000; Mayeux 2003; Tanner et al. 1997; Van Den Eeden et al. 2003). A male bias is found in many studies (Dluzen 2000; Horstink et al. 2003; Tanner et al. 1997; Van Den Eeden et al. 2003), but not in all (de Rijk et al. 2000; Diamond et al. 1990; Tanner et al. 1997). The sex effect may vary ethnically. In a large series from Kaiser Permanente, sex differences were absent in Asian/Pacific Islanders, whereas white, blacks and Hispanics showed a two-fold male bias (Van Den Eeden et al. 2003). Other studies also found ethnic differences (Mayeux 2003; Mayeux et al. 1995). We provisionally conclude that sex differences in AD and PD are smaller than population differences.

Menopause and estrogen replacement

The risks and benefits of estrogen replacement after menopause are hotly controversial. We must keep in mind the extreme case of Mme. Jeanne Calment, who achieved the greatest documented human life span of 122 years, yet was considered to be neurologically healthy. At 118 years of age, Mme Calment tested for neuropsychological performance in the range expected for a healthy 80-year-old (Ritchie 1995). Although no specific tests were given, major motor impairments or Parkinsonism could hardly have escaped notice because of the great attention she received. Assuming a typical age at menopause, Mme Calment lived 70 years in the absence of estrogens, with at least 50 of those years in good physical health. Mme Calment's extraordinary life history cannot be generalized. We do not know whether her uniquely robust constitution also protected her from the effects of postmenopausal deficits that manifestly afflict a substantial fraction of older women.

In contrast to the example of Mme Calment's apparent insensitivity to menopausal estrogen deficits are the clear effects of menopause on cognitive decline in Down's syndrome. As is well known, trisomy chromosome 21 causes very early onset of AD neuropathology in most Down's patients' brains by age 30. However, there are huge individual differences in the onset of cognitive decline, and only a subset of patients show clinical declines (Lott and Head 2001). Of great interest is the finding that early menopause (before age 46) increased the risk of dementia by 2.7-fold (Schupf et al. 2003; Fig. 1). Demented female Down's patients had higher serum sex hormone binding globulin but similar total serum estradiol concentrations. This finding suggests that reductions in free estradiol are a specific factor in the onset of dementia. However, the full explanation

Fig. 1. Early menopause increases the risk of dementia by 2.7-fold (Schupf et al. 2003).

is likely to be more complex, because male Down's patients have a three-fold higher incidence of dementia overall than do females (Schupf et al. 1998).

Estrogen replacement therapy is highly controversial in relation to AD and vascular dementia. On one hand, numerous post hoc observational studies are consistent in citing the benefits of long-term ERT in reducing the risk of dementia (Paganini-Hill and Henderson 1994; Breitner and Zandi 2003; Lamberts 2003; Sherwin 2002). The benefits of ERT may also extend to stroke (Wise 2002). One of these studies is the Cache County (Utah) observational study of all drug use and dementia, which showed a duration-dependent benefit in women who, in the majority, were taking only estrogen (not ERT plus progesterone; Breitner and Zandi 2003). More than 10 years of ERT provided the greatest risk reduction. Animal model studies also generally show benefits of estrogen (Sherwin 2002; Wise 2002). In contrast, an interim report on the Women's Health Initiative Memory Study (WHIMS) showed statistically strong negative effects of an increased incidence of dementia (odds ratio, two-fold) during a randomized trial of equine estrogens plus medroxyprogesterone, with average exposure of four years (Shumaker et al. 2003). Most of the dementia was considered to be probable AD. The effect was equivalent to an increase of 23 cases of dementia/10, 000 women/ year. However, this study also clearly showed adverse cardiovascular effects that could be independent contributors to AD-type dementia, as discussed by Sparks et al. (2000). Many explanations are being considered: in brief, the necessity of prolonged replacement (Breitner and Zandi 2003); the special characteristics of women who voluntarily take estrogen and who tend to be highly educated and have high income, each of which is health promoting; but, also possible adverse effects of medroxyprogesterone, a synthetic progestin with adverse effects on neurons differing from natural progestins (Brinton and Nilsen 2003).

Discussions have also been held about possible benefits of ERT in PD, but much fewer data are available. Again, benefits are indicated by some observational studies of women taking ERT. In older PD patients, the following results were reported: ERT improved motor performance (Benedetti et al. 1998; Saunders-Pullman et al. 1999); ERT improved cognition, but not motor performance (Thulin et al. 1998); and ERT improved cognition in PD, but did not lower the risk of PD (Marder et al. 1998). So far, no controlled trial has been reported. In premenopausal PD patients, one study found sharp increases of motor symptoms just before menstruation, when estrogen and progesterone are dropping sharply (Quinn and Marsden 1986), whereas a more detailed study did not find any consistent relationship between motor symptoms and cycle stage (Kompoliti et al. 2000). Rodent models clearly show that estrogens are neuroprotective for dopaminergic neurotoxicity (MPTP and kainate; Dluzen 2000; Miller et al. 1998; Rostene et al. 2003).

It is fair to say that the divergent and perplexing findings on ERT imply a complex biology of estrogen's effects on different neural pathways and on the

cerebro- and myocardial vascular systems. We suspect that several other factors are pertinent and have not been adequately considered: aging and the schedule of prior estrogen exposure.

Aging modifies brain responses to estrogen

Neuronal plasticity is modulated by estradiol in many brain systems. Synaptic sprouting in the hippocampus is induced by perforant path lesions, which are models for degeneration of this pathway during AD (reviewed in Stone et al. 2000). In young adult rats (three months), ovariectomy decreased sprouting relative to intact or estradiol-replaced rats (Fig. 2). However, in middle-aged rats (18 months), sprouting was less and was not influenced by ovariectomy (Fig. 2). We are investigating the cellular basis for this age change using the "wounding-in-a-dish" model of sprouting. Astrocytic GFAP (the intermediate filament) has a negative effect on sprouting that is reversed by estradiol treatment, which represses GFAP transcription (Rozovsky et al. 2002). We hypothesize that the elevation of GFAP expression that occurs during normal aging (Finch et al. 2002; Miller et al. 1998; Morgan et al. 1999; Nichols et al. 1993) is a factor in impaired sprouting. Astrocytes derived from middle-aged rat cortex support notably less neurite outgrowth in the presence of estradiol, which implicates aging in astrocytes as a factor in the impairments of estradiol-sensitive sprouting (Fig. 2). Down regulation of GFAP by SiRNA restored the ability of aging astrocytes to support sprouting of E18 neurons (Rozovsky et al., manuscript in press). Further

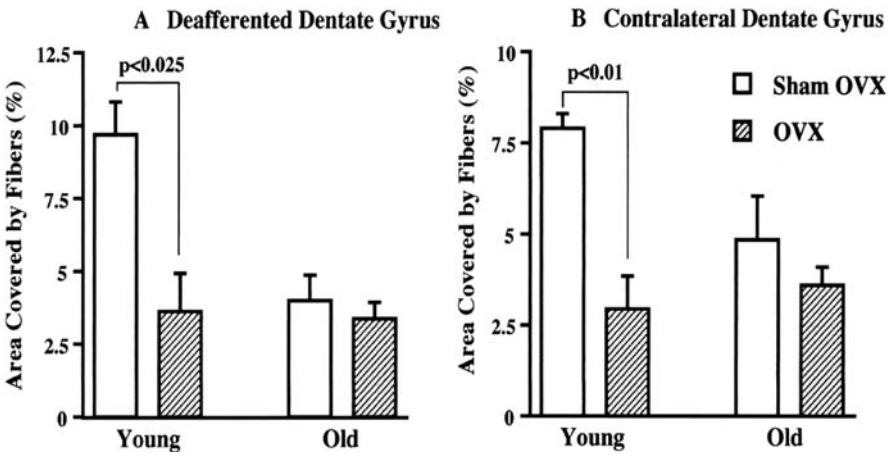

Fig. 2. Aging decreases responsiveness of synaptic sprouting to estradiol (E2) in a rat model of AD (perforant path lesion-induced sprouting, as observed in AD; Stone et al. 2000). OVX, ovariectomized.

studies are needed to establish the consequences on neuronal functions of the general induction of GFAP in most brain regions during aging.

Other brain regions also show age impairments in the responses of neurons to estradiol. In the olfactory bulb, estradiol induced the neurotrophin receptor TrkA in young, but not in middle-aged, female rats (Jezierski and Sohrabji 2001; Fig. 3). Moreover, BDNF mRNA and protein were induced in the olfactory bulb and its forebrain afferent by estradiol in the young, but not in the middle-aged; in the latter, a decrease was observed (Jezierski and Sohrabji 2001). The age impairments in estradiol regulation of trk receptors could alter neurotrophin transport and signal transduction pathways. Besides these modulations of synaptic plasticity, estradiol is also recognized as neuroprotectant to MPTP in dopaminergic neurons (model of drug-induced Parkinsonism; Miller et al. 1998; Rostene et al. 2003). In contrast to the neuroprotection to systemic MPTP shown in two-month-old mice, estradiol did not block the loss of dopamine in 24-month-old mice or the induction of GFAP (Miller et al. 1998; Fig. 4). These observations suggest that age changes in estradiol levels could reduce endogenous neuroprotection. Estrogens and estrogen receptor modulators are also neuroprotective to excitotoxins in glutamatergic neurons (O'Neill et al. 2004). Thus, the diminishing levels of estradiol in the cerebrospinal fluid (CSF) after menopause (Murakami et al. 1999) could be important in the increased risk of neurodegeneration. AD patients have lower CSF estradiol than controls (Schonknecht et al. 2001). If the age change in estradiol neuroprotection extends to other brain regions, then age may bring a double jeopardy to neurons:

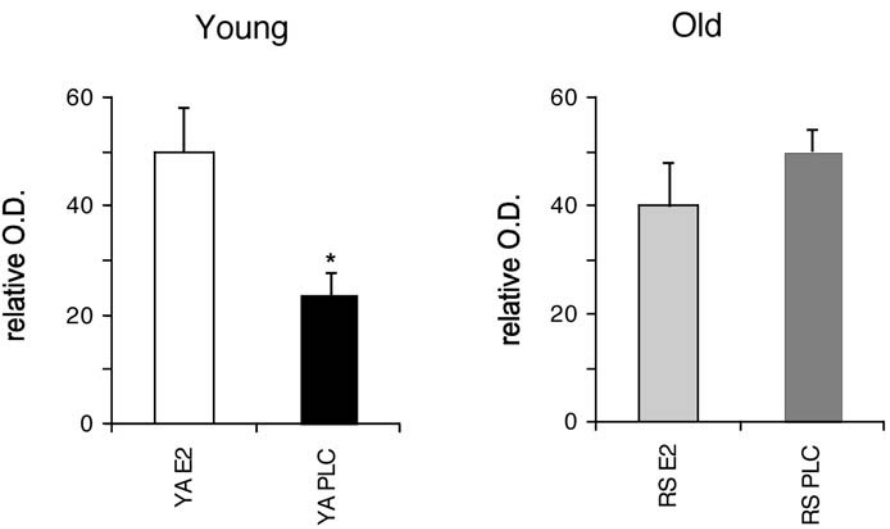

Fig. 3. Aging impairs the inducibility of Trk A in the olfactory bulb of the female rat (Jezierski and Sohrabji 2001).

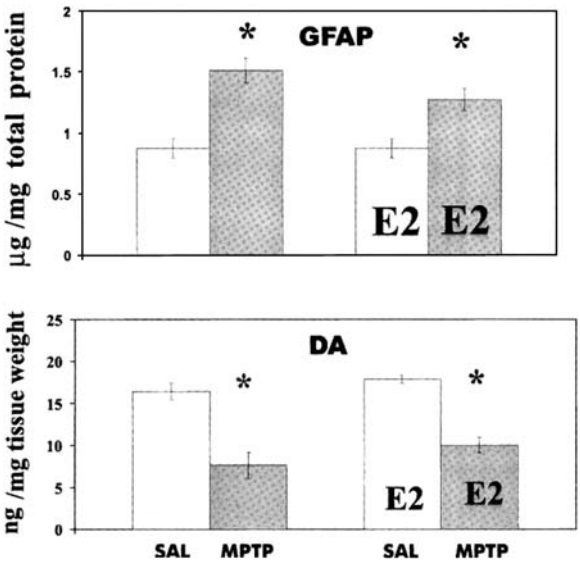

Fig. 4. Aging impairs neuroprotection by estradiol (E2) to MPTP neurotoxicity, a model of drug-induced PD (Miller et al. 1998). DA, dopamine. GFAP, Glial Fibrillary Acidic Protein.

decreased endogenous neuroprotection by estradiol with further adverse effects from the reduced neuroprotection.

Estrogen exposure as a factor in aging of brain cells

The role of estrogen exposure in loss of estrogen responses during aging is indicated by studies on the neuroendocrinology of aging from two decades ago. Female rodents show a characteristic pattern of reproductive aging during their life spans of about 30 months (Fig. 5). (For general references on the following profile, see vom Saal et al. 1994; Wise et al. 1999; Gosden and Finch 2000). In rodents as in humans, the ovary has acquired its maximum store of oocytes and primary follicles before birth and no new oogenesis occurs during the rest of life. Oocyte depletion shows exponential decline from birth onwards, so that by puberty, about 50% of the original stock of oocytes is already lost. Fertility declines in rodents by eight months and in women after 30 years (long before the depletion of oocytes and hormone-producing follicles). Estrous cycles tend to become progressively longer and finally cease between 8 and 16 months. Nonetheless, the acyclic ovary has a substantial number of estrogen-secreting follicles that give a vaginal cytology described as "constant estrus." The basis for this loss of cycles in rodents is hypothalamic, because total depletion of ovarian oocytes and follicles does not occur for several more months (Gosden et al. 1983). Reciprocal ovarian transplants in still-cycling 12- and 3-month-old mice show, at this intermediate stage of aging, impairments at both ovarian and

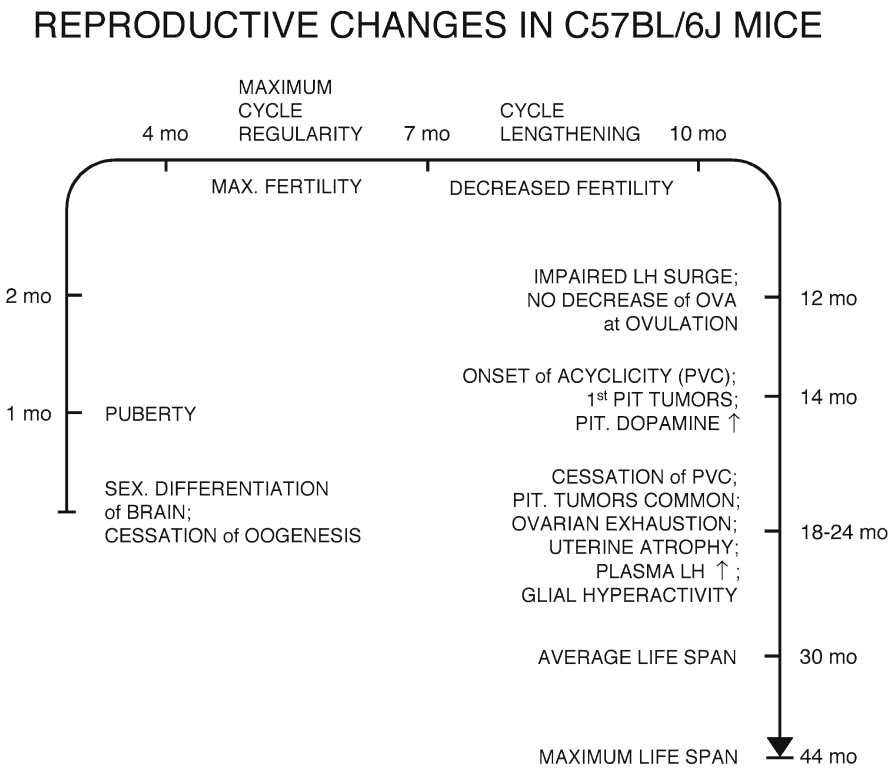

Fig. 5. Reproductive maturation and aging during the life span of inbred C57BL/6J mice. Original figure by Caleb E. Finch summarizing vom Saal et al. (1994). PIT, pituitary.

hypothalamic levels (Nelson et al. 1992). The hypothalamus shows a progressive loss of the preovulatory surge of gonadotrophins (LH, FSH), whether autogenous (in the presence of the aging animal's ovaries) or induced in ovariectomized animals with standard treatment of estrogen and progesterone.

These major hypothalamic impairments are further documented by the failure of young ovarian grafts to restore estrus cycles (Finch et al. 1984). However, if young ovaries are given to middle-aged mice just before cycles have ceased, then cycles continue for many more months (Fig. 6). Our hypothesis is that the hypothalamus becomes desensitized during the lengthened cycles as constant estrus is approached. This phase is characterized by sustained levels of estradiol and very low levels of progesterone. Similar estrogen-dominated prolonged cycles are observed before menopause (Santoro et al. 1996; Fig. 7). To model this phase, we developed a noninvasive administration of oral estradiol (Kohama et al. 1989; Fig. 8). Time-dose studies showed that 12 weeks of low physiological levels of estrogen in young mice caused permanent neuroendocrine

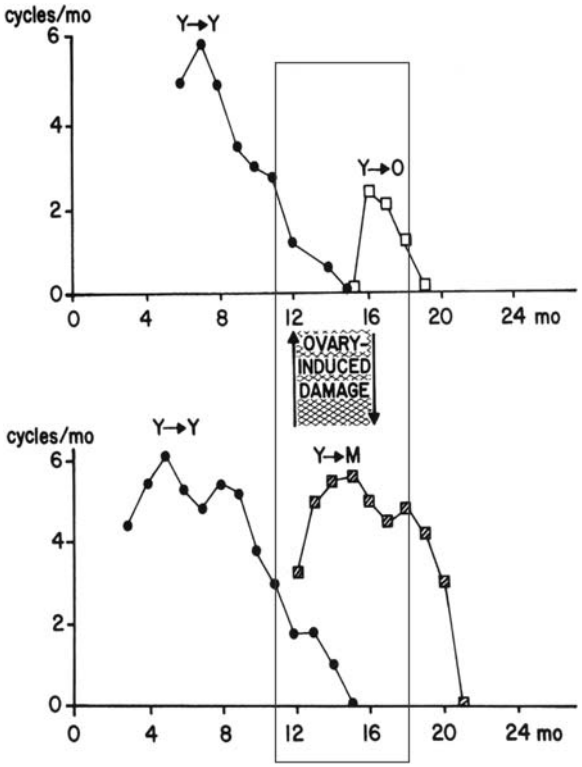

Fig. 6. Grafts of young ovaries to replace aging ovaries of middle-aged mice just before cycles have ceased allow regular ovulatory cycles to continue for many more months (Finch et al. 1984).

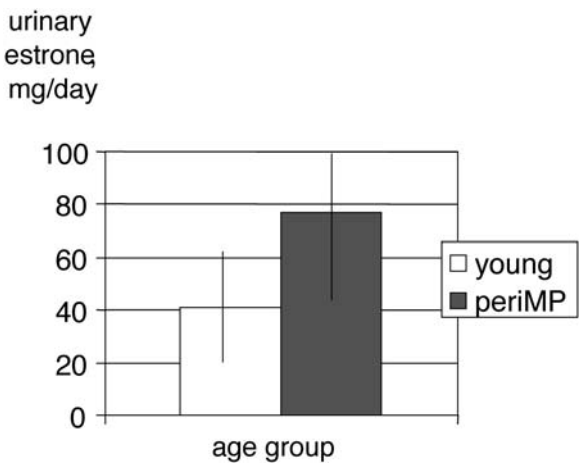

Fig. 7. Estrogen-dominated prolonged cycles are also observed before menopause (peri-MP; Santoro et al. 1996).

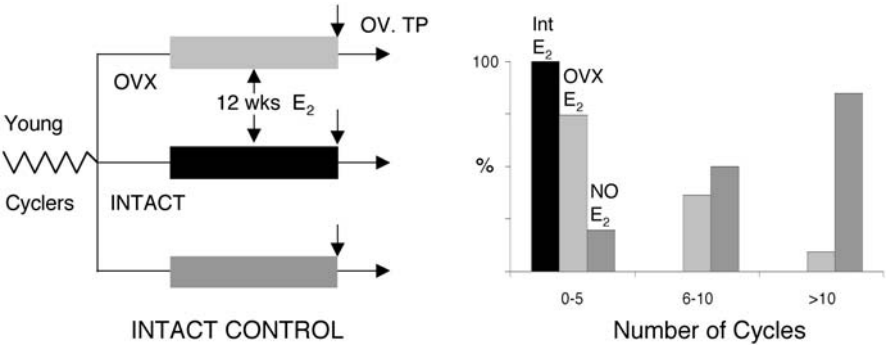

Fig. 8. Oral estrogens yield low physiological levels of estrogen in young mice and cause permanent neuroendocrine impairments. Redrawn from Kohama et al. (1989).

impairments, so that the LH/FSH surge could no longer be induced; neither could grafting of young ovaries from control mice restore cyclicity (Kohama et al. 1989). With a shorter exposure for six weeks to low-dose estradiol, mice regained cycling but then ceased prematurely. We estimate that 3500 pg-day/ml plasma is sufficient to cause permanent hypothalamic desensitization, within boundary levels of approximately 10-30 pg estradiol/ml plasma.

Of course, these rodent model studies cannot be simply extrapolated to humans. Nonetheless, the irreversible effect of sustained physiological levels of estradiol on the hypothalamic regulation of LH/FSH provides a model for studying specific cellular targets of estrogen regulation, such as age-related changes in estrogen-mediated synaptic sprouting (Fig. 2), TrkA induction (Fig. 3), and neuroprotection (Fig. 4).

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